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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/556,941	04/21/2000	Karen Heichman	2318-261	6422

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/556,941	Applicant(s) HEICHMAN ET AL.
	Examiner Dave Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *5-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Applicant's election of Group I claims (claims 1-4, 44-45) directed to the specifically named complex of IRAP (Insulin regulated Membrane-Spanning Aminopeptidase) and PTPZ (protein tyrosine phosphatase zeta) in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed error in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-4, 44-45 are objected because the claims contains non-elected subject matters Applicant must amend the claims so as to be readable only on the subject matter directed to the invention of the IRAP-PTPZ complex. Presently, non-elected subject matters as embraced by claims 1-4, 44-45 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 5-43 also have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Appropriate correction is required.

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-4, 44-45 are rejected under 35 U.S.C. 101 as the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Applicant is directed to the Revised Interim Utility Guidelines, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999. In keeping with the revised utility guidelines and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific, credible and/or substantial use.

The specification discloses a complex or interaction or binding between IRAP (Insulin regulated Membrane-Spanning Aminopeptidase) and PTPZ (protein tyrosine phosphatase zeta) (page 18, Table 67; page 57, example 67) by using a yeast two-hybrid assay. Applicant suggested that these protein-protein interaction are involved in mammalian physiological pathways, including physiological disorders or diseases (Page 1, paragraph 2); that identification

of agents which are capable of modulating the interaction will provide agents, which can be used to track the physiological disorder, or use as lead compound for development of therapeutic agents(pages 3-4); and that identification of these interaction enables the development of diagnostic assays and kits, which can be used to determine a predisposition to or the existence of physiological disorder. These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or specific biological significance for the protein complex comprising the full-length IRAP and PTPZ, let alone complexes embracing fragments thereof. Specification fails to disclose an association of protein complex comprising the full-length IRAP and PTPZ with any physiological disorders or diseases. In addition, specification does not provide any information about presence of any of IRAP/PTPZ complexes in mammalians. Moreover, the state of the prior art exemplified by Nishiwaki *et al.* (Keio University Symposia for Life Science and Medicine, 2 (Neural Development), pp. 291-297, 1999; J. of Biological Chemistry, 123, 3, 458-67, 1998, abstract) indicates that while PTPZ are known to be expressed in the brain, PTPZ(s) are expressed in different isoforms and are involved in complex physiochemical interactions, which are dependent on a particular stage of development and/or a biological pathway (abstract). More specifically as to the complexity of PTPZ that appears to interact with proteins other than IRAP, Kawachi *et al.* (Brain Research Molecular Brain Research, 72, 1, 1999, 47-54) teaches that by using the very same yeast two-hybrid screening assay, they observed that the C-terminal sequence of PTPzeta binds to the PSD-95/SAP90 family through the second PDZ domain, and that PTPzeta and PSD-95/SAP90 are similarly distributed in the dendrites of pyramidal neurons of the hippocampus and neocortex (abstract). Another skilled artisan (PNAS, Vol. 98, 12, 6593-8, 2001) reaffirms the complex physiobiochemical function of PTPzeta by showing that PTPzeta also interacts with other proteins including those of T protein-couple receptor kinase-interactor 1/Cool-associated, tyrosine-phosphorylated 1 (GIT1/Cat-1) in a yeast-two hybrid assay.

Notwithstanding the complexities of PTPzeta and its role in *in vivo* biochemical interactions, the state of the prior art exemplified by Keller (International Congress Series, 1218 (Cell-Surface Aminopeptidases: Basic and Clinical Aspects), pp. 243-250, 2002) indicates that while IRAP is known to be a major protein in intracellular vesicles that also harbors the insulin-responsive glucose transporter GLUT4, the ***in vivo* substrates for IRAP are unknown,** and that

the physiological function of IRAP and the role it plays in insulin action remains to be determined (abstract).

As such, the prior art of record demonstrates that the biological function of the protein family to which the disclosed protein is said to be a member is so diverse, that one could not predict which biological activity is possessed by the disclosed protein complex based on the state of the prior art with respect to **the already complex** physiological function of each of the two proteins, and that the yeast two hybrid assays with respect to PTPzeta appears further shows distinct binding results if not conflicting, wherein the results are further needed to be further experimented in order arrive at a substantial, credible and specific use of such complex including the claimed complex. In light of this evidence, one skilled in the art would not conclude that the disclosed utilities appear to be either specific or substantial because the specification fails to disclose a specific and substantial credible utility for protein complex as claimed. Therefore, protein complex comprising IRAP/PTPZ appear to constitute research reagents for further experimentation to discover a "real-world" utility for the claimed invention.

In addition, since protein complex comprising IRAP/PTPZ itself appears to constitute a research reagent, protein complex comprising fragments of proteins or a fragment of one protein and a complete protein of another protein also do not appear to have a specific and substantial credible utility, or a well established utility.

Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001

As such, further research would be required. See *Brenner v. Manson*, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), the court indicates "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 44-45 also rejected under 35 U.S.C. I I2, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, since the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, the specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only "protein complex comprising IRAP/PTPZ. The instant claims encompass in their breadth (1) any fragment of protein IRAP/PTPZ or (2) a complex comprising any fragment of each of IRAP or PTPZ that may bind to other corresponding active protein, *e.g.,* PTPZ or IRAP. The specification fails to provide guidance as how to make and use any fragment of IRAP/PTPZ without undue experimentation. There is not sufficient guidance in the specification as filed so as to show how a skilled artisan would make and use the various fragments of protein IRAP/PTPZ or fragments of each of the proteins when used within the context of a IRAP/PTPZ complex. A person of skill in the art would not know which sequences are essential and which sequences are non-essential. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for the function of IRAP/PTPZ. In addition, the term "comprising" in the claims is open-ended, wherein it expands "the fragment of IRAP/PTPZ to include additional non disclosed amino acids. Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, any fragment of the IRAP/PTPZ complex encompassed by the claimed invention would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional

properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. IRAP/PTPZ) requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i e expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of IRAP/PTPZ and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation, *e.g., In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to IRAP/PTPZ with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The protein Folding problem and Tertiary Structure prediction 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of protein complex encompassed by the claimed invention. The instant disclosure fails to provide sufficient guidance or working examples on how to practice the claimed invention. The general information on how to perform a screen assay and how to identify a modulator of protein interaction, as provided in the specification, cannot be used as a guidance to practice the instantly claimed invention.

Although one skilled certainly has the technology and skills to perform a method for screening drug candidate, the fact that there is no direct interaction established in the art between these two proteins in the art indicates the complexity and unpredictability of practicing the instantly claimed invention. Since there is no sufficient guidance to make and use the claimed

invention, it would take undue experimentation for one skilled in the art to practice the instant invention.

In addition, without sufficient guidance, the changes which can be made in the structure of IRAP/PTPZ and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER